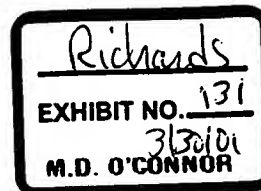




C.W. Orgell, Ph.D.  
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Amoco Technology Co.  
305 East Shuman Blvd., Suite 600  
Naperville, Illinois 60540

December 15, 1989



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C. W. ORGELL

Dear Dr. Orgell:

Pat Connoy has asked me to write to you to outline potential valuable assets which are owned entirely by either Amoco or GENE-TRAK and which require a modest outside research effort to demonstrate technical feasibility and possibly product concept feasibility. In all three cases, patent applications have been prepared and filed which either cover the method or process. Originally, I had intended to present these concepts to the Biotechnology group (Ken Cruickshank et al.) during a scheduled visit on December 12, 1989, but this visit was canceled by Amoco.

Technology Asset #1-Target and background capture methods with amplification for affinity assays (USSN 922,155). This application relates to the so-called "Collins Application" which is background reduction in a nucleic acid hybridization assay. The primary patent was prepared and filed by A.J. Janiuk on October 23, 1989. A CIP to this application was filed about a year later which included inventive material relating to target amplification following target capture and was conceived at Amoco by King, Halbert and Lawrie. In essence, one round of target capture and release results in a highly enriched population of target DNA molecules compared to non-target or background DNA molecules. Random hexanucleotides are then allowed to anneal to multiple sites along the length of all DNA molecules contained in the target DNA-enriched sample. All primer-template complexes become substrates for the Klenow fragment of DNA polymerase I. The enzyme synthesizes new DNA by incorporating nucleoside monophosphates at the free 3'-OH group provided by the primer. The newly synthesized DNA can serve as template for subsequent cycles of such an amplification process. One can envision using the Stratagene Cloning System i.e., Prime-It™ Random Primer Kit which uses T7 pol and random primers to achieve the same goal much faster. Obviously, in both cases, temperature cycling would be required to obtain multiple copies. Another approach would be to use a transcriptase capable of initiating from a random promoter or primer and thus giving rise to 10->100->1000 RNA copies per recognized DNA template.

131

December 15, 1989

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The important concept in this invention is that without target enrichment one would amplify noise or background polynucleotides in proportion to target polynucleotides and thereby gain nothing. Cetus, Sibia/Salk, Biotechnica, etc. all claim **specific** primers for amplification whereas the present invention claims use of the opposite, namely, **non-specific** primers or promoters. Consequently, target enrichment becomes the enabling aspect of the amplification method. In practice, one would hybridize targets with a specific poly(A)-tailed capture probe, retrieve hybrid complexes by binding to oligo (dT) support and wash away non-hybridized polynucleotides. Following extensive washing, captured target polynucleotides could be released and the non-specific amplification process could take place. After amplification (10-100X) the polynucleotide containing solution could be subjected to 2-3 rounds of target capture and release using A-tailed capture probes and MDV-1 label probe and finally detected using the Q $\beta$  replicase real time fluorescent detection system. I believe such an approach could have significant value in the area of blood bank screening or any application where there is a very critical need for exquisite sensitivity e.g., <10 molecules/specimen. GENE-TRAK is confident that we can achieve 500-1000 molecule sensitivity with target cycling and Q $\beta$ -smart probes but we will always be limited by the amount of original target polynucleotide present in the sample.

I would add that this application would also eliminate possible GenProbe patent problems since we could target DNA rather than ribosomal RNA. Obviously there are many questions which must be addressed but I feel that a successful reduction to practice of this invention would have great value for GENE-TRAK and Amoco. -Furthermore, since the patent application was filed by Amoco, a successful reduction to practice properly falls within the scope of Amoco Biotechnology research and development.

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December 15, 1989

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We are interested in reviewing these projects with Amoco biotechnology at your earliest convenience. GENE-TRAK was planning to allocate resources to these projects but our 1990 budget has made that very difficult. If Amoco is unable to allocate resources, GENE-TRAK will actively seek outside funding or co-development partners were appropriate. I would appreciate your consideration of these matters and comments, and as mentioned at the beginning of this letter, I would be pleased to present these concepts to you and your staff. Finally, I look forward to meeting you in the future.

Thank you in advance for your consideration of this information and on behalf of GENE-TRAK Systems I wish you and your organization the very best of Holiday greetings and a Happy (and successful) New Year!

Sincerely,



James C. Richards

Director,

Business Development & Licensing

cc

Patrick J. Connoy, GENE-TRAK Systems

Bruce Neri, GENE-TRAK Systems

G.P. Royer, Amoco Technology

J. Triebe, Amoco Technology

E. Jones, Amoco Technology

R. Carpenter, Genzyme Corp.

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